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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/804,762	03/19/2004	Yan Qi	A-72186/TAL/DCF	8100

32940 7590 08/23/2007

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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
08/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/804,762	QI ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5,6,14,15,17-26,33-37 and 39* is/are pending in the application.

4a) Of the above claim(s) *18-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5,6,14,15,17,33-37,39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5/25/07 has been entered.

Claims 16 and 38 are cancelled.

Claims 1, 5-6, 15, 17, 33-35, 37, and 39 are amended.

Claims 1, 5-6, 14-15, 17-26, 33-37, and 39 are presently pending.

Notice Regarding Proper Claim Identifiers

It is noted that several of the presently amended claims are marked as "previously presented", e.g., Claims 1, 5, and 6. While such typically requires a notice of improper amendment practice, the Examiner has decided not enter the claims as they are presented in the interest of compact prosecution. However, Applicant is forewarned that future amendments will be responded to with a notice of non-compliant amendment.

Election/Restrictions

Claims 18-26 remain withdrawn as being drawn to non-elected inventions.

Claims 1, 5-6, 14-15, 17, 33-37, and 39 are presently considered.

Claim Status, Cancelled Claims

In light of the cancellation of Claims 16 and 38, all objections and/or rejections of such claims are withdrawn, as they rendered moot.

Claim Objections

The objections to Claims 15, 37, and 39 under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple dependent claims, are withdrawn.

To wit, the multiple dependency problems have been corrected by the amendments, and therefore, Claims 15, 37, and 39 are again considered on their merits, along with the rest of the claims .

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 14, 15, 17, 33, 36, 37, and 39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 14, 15, 17, 33, 36, 37, and 39 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: those steps required to provide the development of a T cell activation.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 14, 15, 17, 33, 36, 37, and 39 are newly rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. Steps critical or essential to the practice of the invention, but not included in the claim(s) are not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). Applicant's claims are drawn to inhibition of an adaptive T cell response, however, at no point in the claims is there a step to exposure of such cells/tissues to an allogenic tissue which could mount an adaptive T cell response, and such is described throughout the specification as the purpose of such method, and the only way such a response which can be inhibited is brought about.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

While the previous rejections of Claims 1, 5-6, and 33-36 for enablement are withdrawn for various aspects,

Claims 33-37 and 39 are newly or remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of IV injection prior to

transplantation, does not reasonably provide enablement for IV injection *in vivo* (all rejected claims), and IV injection *in vivo* beyond 2-days post-transplant or later. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

It is noted that several claims are now found enabled (i.e., Claims 1-3 and 5-6). With regard to the withdrawn aspects of the rejection, it is noted that paragraph 069 of the specification indicates that the smallest portion of the CD8 molecule is the HLA binding domain, which is found within the Ig-like domain. Further the structure of CD8 alpha chains is also well known, such that the Artisan would be able to determine the functional portion without undue experimentation. With regard to the immune responses, the amendment to adaptive immune response of T cells now negates this point, and it is the development of the adaptation that is inhibited.

The rejections held for reasons of record are now re-explained.

With regard to Claim 33, the claim encompasses *in vivo* and *ex vivo* administration, by IV methods, wherein just injection is proximal to the cells. Still further, Claim 33 encompasses administrations 2 or more days after transplantation.

With regard to Claims 34-35, the claims encompass administrations, by IV methods, wherein the injection is proximal to the cells.

Claims 36, 37, and 39 are dependent, in the alternative, from Claims 33-35, and do not alter these aforementioned IV injection methods and times. Hence, they similarly encompass these same aspects.

To make this clear, Claim 33 requires intravascular injection proximal to the target cells, and makes no stipulation when the cells are transplanted, and hence encompass transformation prior to, during or any point after transplantation. Still further, no claim is made as to when the cells were induced to express such alloantigen, as compared to the time the administration of the IV injection is made and hence, the claim encompasses time frames more than 2 days after expression of the alloantigen within the body.

Claim 34 requires the IV injection to be made prior to, or contemporaneous with transplantation, and hence, is not subject to the later than 2-days post transplant rejection. However, the claims still encompass IV injection *in vivo*, which is rejected for this aspect. Such is because the injection can be after the attachment of any vasculature to the transplanted tissue, but prior to closing up the subject's body, and such would still be contemporaneous.

Claim 35 encompasses only contemporaneous IV administrations proximate to the allograft, however, for the same reasons as given for Claim 34, such claim encompasses IV injection *in vivo*.

Claims 36, 37, and 29 each depend in the alternative, from 33-34, and thus encompass the scopes of each independent claim.

With regard to in vivo transfection of these cells via IV injection proximal to the target cells, as has been previously discussed, it is not reasonably predictable that enough cells are transformed in any particular case (Official Actions of 11/30/06, p. 5 and 5/2/06, pp. 6-7). To recap, the prior art demonstrations that in any particular administration, it is not reasonably predictable that enough tissues will be transformed to have an effect. Further, Applicant's own examples demonstrate that particular tissues are refractory to transformation by any particular

vector (EXAMPLE 3), and the various examples only demonstrate long-term incubation (multiple hours) in the presence of the vector. It is noted that the basis of rejection for refractory transformation are withdrawn on their own, as the Artisan would understand which tissues could be transformed with any particular vector type, however, such necessarily demonstrates the well-known differences in transfection ability of any particular cell type, providing a range of sensitivities. Hence, because an IV injection, proximate to the site would necessarily encompass injection into the arterial/venous system at any point, because the blood would necessarily pass through the arteries and veins of the transplanted cells, but because any particular tissue will have any particular affinity for the cells, such a quick pass through the tissue in the blood would not reasonably be predicted to transform enough cells. Further, for Applicant's specifically discussed adenoviral vectors, such would likely be cleared by the liver before reaching the tissue in most administrations and/or cleared after the first pass through the organ. Further, in the best case scenario, that of injection in the artery(s) directly upstream of the organ, such a quick pass through the organ would not be reasonably predicted to transform enough cells, and would therefore have to pass through the rest of the body before reentering the organ, without transforming other tissues or being cleared by the liver/kidneys/macrophages of the body, in order to continue transformation to get enough cells transformed. Such is exacerbated by the fact that certain tissues directly transformed do have an immune response due to lack of enough cells being transformed (EXAMPLE 3). Applicant's explanation of a barrier (e.g., Declaration by Dr. Staerz of 9/29/06) fails to overcome this aspect, because the requisite number of cells still need to be transformed for any particular transplant.

With regard to transformation of cells beyond 2 days post transplantation of the cells expressing alloantigens, as has been previously stated, Sambhara, et al. (1991) Science, 252: 1424-27, pp. 1424-25, paragraph bridging, indicates that the development of the T-cell response occurs during the first two days (Official Action of 11/30/06, p. 4). Hence, it would not be reasonably predicted to work to inhibit adaptation beyond the first 2 days.

Hence, the Artisan would have to experiment to determine those transplantation which could be treated by any particular IV injection, and at any time post-2 days of transplant.

Such amounts to undue experimentation as it amounts to the claimed subject matter for Applicant.

As such, the claims are rejected for not being fully enabled.

Response to Argument – Enablement

Applicant's argument of 11/30/07 has been fully considered but is not found persuasive.

Applicant's arguments to inhibiting fully-activated T-cells is noted, but irrelevant because they do not claim inactivation of fully-activated T-cells, but only the development of adaptive immunity (Argument on pages 8-9).

Applicant argues that Sambhara, et al. (1991) Science, 252: 1424-27 does not reflect *in vivo* application of the method, citing the 5/25/07 declaration of Dr. Steaerz, which states that kidney cell rejection showed little reactive T cells at day 2, but a massive response at day 5, and as such the rejection for 2-day limit is not proper (p. 10 of argument, paragraph 10 of the declaration).

Such is not persuasive. First, it is shown that there are reactive T cells at day 2, so the question becomes whether or not the massive response is due to migration of new T-cells or the

proliferation of the already activated T-cells at day 2. Still further, at the very least, even if it were proved that the response is due to further migration, whether or not such is the same for every tissue. In such a case, the Artisan would have to experiment to determine the time frame for any particular development of response. In either case, it amounts to undue experimentation for any particular tissue, and the common result of 2 days having responding T cells demonstrates that the adaptive response is already developed and is not inhibited.

Applicant argues that certain tissues, even though refractory, are still enabled (p. 10).

Such is persuasive on its own, as the Artisan would know which tissues could be transformed.

Applicant argues that various techniques have been proposed in the Art including kidney loading and recycling after kidney pass-through, citing the same in the declaration of Dr. Staertz of 5/25/07 (pp. 10-11, paragraph briding, and Staertz Declaration of 5/25/07; paragraph 13).

Such is not persuasive. First recycling after kidney pass-through is the same as perfusion of the organ, however, Applicant's claim encompass injection at a point "proximate" which is intravenous, and as such encompasses more than perfusion of the organ, but any injection which is IV. With regard to recycling, such is not taught in the specification, and nothing would lead the artisan to that technique. With regard to kidney loading, again nothing in the specification limits this method to such a method. Moreover, none of the methods are even limited to kidney. Lastly, although various fantastic techniques could be envisioned, given the enablement, the Artisan would find it undue experimentation to determine if they would work in any particular case.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5, 6, and 14 remain rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent Application No. 2002/0127205 to Edge, et al, for reasons of record, and as explained below.

With regard to Claims 1, 5, and 6, Edge teaches compositions comprising genetically modified to express molecules which inhibit T-cell activation and can be used for transplantation (ABSTRACT; paragraph 0009). Such transgenically expressed proteins include the whole CD8 (paragraph 0009). Moreover, graft survival can be extended (paragraph 0006) (See Also, Claim 1). Moreover, ex vivo perfusion techniques are taught (e.g., paragraph 0146).

To wit, with regard to Claims 14, 15, and 17, Edge discloses human CD8-alpha, in paragraph 0059, where reference is made to Shiue, et al., for the CD8-alpha. Shiue teaches human CD8, including CD8-alpha chains. (The reference to Shiue, et al. (1988) J Exp Med, 168(6): 1993-2005 is attached for Applicant's convenience.)

Response to Argument – anticipation, Edge

Applicant's arguments of 5/25/07 have been fully considered but are not found persuasive.

Applicant argues that their claims have been amended to recite "a CD8 polypeptide consisting essentially of all or a functional portion of a CD8 alpha-chain, wherein said CD8

alpha-chain includes a transmembrane domain for expression of said CD8 alpha-chain on the surface of said target cell" overcomes the anticipation rejection because it excludes the beta-chain (p. 11, paragraph 4).

Such is not persuasive. The MPEP states that when the transitional phrase "consisting essentially of" is to be considered in a claim, the specification is looked to in order to determine what is excluded (MPEP 2105). While such necessarily excludes such things from the composition which are clearly detrimental (e.g., cyanide), the specification at no point makes clear that such terminology is meant to exclude the beta-chain of the CD8 molecule. In fact, most of the references in the specification make clear that the beta-chain may be included (e.g., paragraph 0069), and while the terminology "functional portion" indicates that portion comprising the alpha-chain portion which is active (Id.), it is not stated anywhere that consisting essentially of excludes the beta-chain.

Applicant argues that the conventional view in the Art required the whole CD8 molecule, and Edge teaches the whole CD8 molecule, and further teaches using a human genetic DNA construct, which results in both membrane bound and soluble forms of the protein, and hence, their claims are distinguished from Edge (p. 11, last paragraph, citing paragraphs 4-7 of the Staertz declaration).

Such is not persuasive. First, with regard to the whole CD8 molecule, as established above, Applicant's claims encompass such. Second, with regard to membrane bound as well as soluble forms, Applicant's claims encompass Edge's invention because of the comprising language and the fact that Edge does have membrane bound forms of CD8, as admitted by Applicant. Third, however Edge's invention works, there is no showing that the Artisan would

not believe this invention to work. To wit, extensive argument is provided by the Staertz declaration and Applicant's argument as to what was thought in the Art, but there is no showing that any particular mechanism does not work; only showings that particular forms do work. Hence, there is no reason to believe it would not work. Lastly, it should be noted that the references cited in the Staertz declaration were not supplied to the Examiner, and no recitation is provided as to where in the references such demonstration of distinct mechanisms are present such that the Artisan would not understand the invention not to be encompassed by the prior Art. As such, the Examiner cannot determine whether or not these references demonstrate the inoperability of the method of the prior Art or not.

Applicant argues that the Art generally demonstrates that it was not previously known that the method would work on CD4+ T cells, and hence, it does not anticipate the claims (pp. 11-12, paragraph bridging).

Such is not persuasive. There is nothing in the Claims to limit the method to CD4+ T cells, or even to include CD4+ T cell activation in the method.

Applicant cites MPEP 2121.01 to state that the disclosure must be enabled, and mere naming or description is insufficient if it cannot be produced without undue experimentation (p. 12).

Such is not persuasive. The disclosure is made, there is no reason to doubt it would work. Still further, the methods are provided in the Art to make the invention. Hence, it would appear that the invention is operable and enabled for making.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 5, 6, 14, 15 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by any one of U.S. Patent Nos. 5,623,056, 5,601,828 or 5,242,687, each to Tykocinski, et al.

Each patent is described in terms of the 5,601,828 patent, as they have similar disclosures as per the rejected subject matter.

With regard to Claims 1, 5, and 6, Tokocinski teaches specific and non-specific immunomodulation, enhancement of cellular engraftment, and modulation of non-immune cells achieved by using various membrane-binding and soluble CD8 compositions (e.g., ABSTRACT). Such CD8 is specifically defined in the specification to be CD8 alpha (col. 5, paragraph 3). Further such CD8 may be made in membrane bound form, using either the natural CD8 transmembrane sequence, or using other transmembrane sequences attached to the CD8 alpha functional domain (e.g., col. 7, paragraph 4). Further, such cells may be transformed to express the CD8 molecule on its surface (e.g., col. 11, paragraph 2). Such cells and compositions are taught to suppress T cell activation through the proximity of the CD8 molecule with the alloantigen (e.g., col. 3, paragraph 4). Still further, to enhance allogenic engraftment, the cells are coated with CD8 prior to transplantation, which the Artisan would recognize to

include either the transgenic expression, or the other methods of such coating described in the specification.

With regard to Claims 15 and 17, the human CD8 alpha chains are disclosed (e.g., col. 5, paragraph 4).

Moreover, it is noted that some of the claims in the 5,623,056 patent are drawn to the cells expressing CD8 and the antigen (e.g., Claims 15-19).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 33-36, 37, and 39 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over any one of U.S. Patent Nos. 5,623,056, 5,601,828 or 5,242,687, each to Tykocinski, et al. and Donahue, et al. (1997) Proc. Natl. Acad. Sci., USA, 94(9): 4664-68.

As shown in the anticipation rejections to Tykocinski, above, the various aspects of the invention, except that of IV injection proximal to the organ to transform the cells being transplanted. On the other hand, Tykocinski teaches that ex vivo perfusion techniques can be used to coat the cells of the organ prior to transplant (e.g., cols. 14-15, paragraph bridging).

However, it was well known in the Art to ex vivo perfuse organs with vectors to have transgenic expression of proteins and such is generally enabled for perfusion of organs separate

from the body's circulatory system. One such reference which exemplifies this aspect is Donahue, et al. (1997) Proc. Natl. Acad. Sci., USA, 94(9): 4664-68, e.g., ABSTRACT.

Hence, at the time of invention, the Artisan would have been motivated to perfuse hearts by IV injection into the heart's arteries with the CD8 alpha chains of Tykocinski within the Adenoviral vectors of Donahue. The Artisan would have been motivated to do so in order to suppress T cell activation, as taught by Tykocinski. Moreover, the Artisan would have had a reasonable expectation of success, as Tykocinski taught that the molecules would suppress T cell activation, and Donahue demonstrated the ability to transform all the heart tissue with such vectors by perfusion techniques.

Conclusions

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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